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(57) Abstract

The present invention describes methods for preventing and treating sexual dysfunctions in male and female patients by orally administering at least one α–adrenergic receptor antagonist and at least one compound that elevates endogenous nitric oxide or endothelium–derived relaxing factor *in vivo* or is a substrate for nitric oxide synthase. The present invention also describes orally administrable compositions comprising at least one α–adrenergic receptor antagonist and at least one compound that elevates endogenous nitric oxide or endothelium–derived relaxing factor *in vivo* or is a substrate for nitric oxide synthase. In the present invention, the α–adrenergic receptor antagonist is preferably yohimbine or phentolamine, and the compound that elevates endogenous nitric oxide or endothelium–derived relaxing factor *in vivo* or is a substrate for nitric oxide synthase is preferably L–arginine. In preferred embodiments, the present invention provides a sachet comprising an orally administrable single dose composition of L–arginine and/or a pharmaceutically acceptable salt thereof and yohimbine and/or a pharmaceutically acceptable salt thereof.

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COMPOSITIONS AND METHODS FOR PREVENTING AND TREATING SEXUAL DYSFUNCTIONS

RELATED APPLICATIONS

This application claims priority to U.S. Application No. 09/285,048 filed April 2, 1999.

FIELD OF THE INVENTION

The present invention describes methods for treating sexual dysfunctions in patients by orally administering at least one α-adrenergic receptor antagonist and at least one compound that elevates endogenous nitric oxide or endothelium-derived relaxing factor *in vivo* or is a substrate for nitric oxide synthase. The present invention also describes orally administrable compositions comprising at least one α-adrenergic receptor antagonist and at least one compound that elevates endogenous nitric oxide or endothelium-derived relaxing factor *in vivo* or is a substrate for nitric oxide synthase. In the present invention, the α-adrenergic receptor antagonist is preferably yohimbine or phentolamine, and the compound that elevates endogenous nitric oxide or endothelium-derived relaxing factor *in vivo* or is a substrate for nitric oxide synthase is preferably L-arginine.

BACKGROUND OF THE INVENTION

Adequate sexual function is a complex interaction of hormonal events and psychosocial relationships. There are four stages to sexual response as described in the *International Journal of Gynecology & Obstetrics*, 51(3):265-277 (1995). The first stage of sexual response is desire. The second stage of sexual response is arousal. Both physical and emotional stimulation may lead to breast and genital vasodilation and clitoral engorgement (vasocongestion). In the female, dilation and engorgement of the blood vessels in the labia and tissue surrounding the vagina produce the "orgasmic platform," an area at the distal third of the vagina where blood becomes sequestered. Localized perivaginal swelling and vaginal lubrication make up the changes in this stage of sexual response. Subsequently, ballooning of the proximal portion of the vagina and elevation of the uterus occurs. In the male, vasodilation of the cavernosal arteries and closure of the venous channels that drain the penis produce an erection. The third stage of

sexual response is orgasm, while the fourth stage is resolution. Interruption or absence of any of the stages of the sexual response cycle can result in sexual dysfunction. One study found that 35% of males and 42% of females reported some form of sexual dysfunction. Read et al, *J. Public Health Med.*, 19(4):387-391 (1997).

While there are obvious differences in the sexual response between males and females, one common aspect of the sexual response is the erectile response. The erectile response in both males and females is the result of engorgement of the erectile tissues of the genitalia with blood which is caused by the relaxation of smooth muscles in the arteries serving the genitalia.

In both pre-menopausal and menopausal females, sexual dysfunction can include, for example, sexual pain disorders, sexual desire disorders, sexual arousal dysfunction, orgasmic dysfunction, dyspareunia, and vaginismus. Sexual dysfunction can be caused, for example, by pregnancy, menopause, cancer, pelvic surgery, chronic medical illness or medications.

In males, some pharmacological methods of treatment are available, however, such methods have not proven to be highly satisfactory or without potentially severe side-effects. Papaverine is now widely used to treat impotence. Papaverine is generally effective in cases where the dysfunction is psychogenic or neurogenic and where severe atherosclerosis is not involved. Injection of papaverine, a smooth muscle relaxant, or phenoxybenzamine, a non-specific antagonist and hypotensive, into a corpus cavernosum has been found to cause an erection sufficient for vaginal penetration, however, these treatments are not without the serious and often painful side effect of priapism. Also, in cases where severe atherosclerosis is not a cause of the dysfunction, intracavernosal injection of phentolamine, an α-adrenergic antagonist, is used. As an alternative or, in some cases, as an adjunct to α-adrenergic blockade, prostaglandin E_1 (PGE_1) has been administered via intracavernosal injection. A major side effect frequently associated with intracorprally delivered PGE_1 is penile pain and burning.

There is a need in the art for new and improved treatments of male and

female sexual dysfunctions, particularly treatments that do not have the undesirable side effects of those agents currently used. The present invention is directed to these, as well as other, important ends.

SUMMARY OF THE INVENTION

The present invention provides methods for preventing and/or treating sexual dysfunctions and/or enhancing sexual responses in patients, including males and females, by administering to a patient in need thereof a therapeutically effective amount of at least one α-adrenergic receptor antagonist and at least one compound that elevates levels of endogenous nitric oxide or endothelium-derived relaxing factor (EDRF) *in vivo* or is a substrate for nitric oxide synthase. Preferably, the α-adrenergic receptor antagonist is yohimbine or phentolamine. Preferably, the compound that elevates levels of endogenous nitric oxide or EDRF *in vivo* or is a substrate for nitric oxide synthase is L-arginine. In the methods of the present invention, the compounds may be administered separately or as components of the same composition. The compounds and/or compositions are preferably administered from about 1 minute to about 120 minutes prior to sexual activity or sexual intercourse in order to prevent and/or treat sexual dysfunctions and/or to enhance sexual responses in a patient.

In another embodiment, the present invention provides orally administrable compositions comprising a therapeutically effective amount of at least one α-adrenergic receptor antagonist, and at least one compound that elevates levels of endogenous nitric oxide or endothelium-derived relaxing factor (EDRF) *in vivo* or is a substrate for nitric oxide synthase. The present invention also provides compositions comprising one or more of such compounds in a pharmaceutically acceptable carrier. The α-adrenergic receptor antagonist is preferably yohimbine or phentolamine. The compound that elevates levels of endogenous nitric oxide or EDRF *in vivo* or is a substrate for nitric oxide synthase is preferably L-arginine.

These and other aspects of the invention are described in detail herein.

DETAILED DESCRIPTION OF THE INVENTION

The following definitions may be used throughout the specification.

"Patient" refers to animals, preferably mammals, more preferably humans, and includes males and females.

"α-adrenergic receptor antagonist" refers to any compound that acts as an antagonist to the α-adrenergic receptor.

"L-arginine" refers to the naturally occurring or free base form of arginine.

"Sexual dysfunction" refers to any sexual dysfunction in a patient, including males and females. Sexual dysfunctions may include, for example, sexual desire disorders, sexual arousal disorders, orgasmic disorders and sexual pain disorders. Female sexual dysfunctions refer to any female sexual dysfunctions including, for example, sexual desire disorders, sexual desire dysfunctions, sexual arousal dysfunctions, orgasmic dysfunctions, sexual pain disorders, dyspareunia, and vaginismus. The female may be pre-menopausal or menopausal. Male sexual dysfunctions refer to any male sexual dysfunctions including, for example, male erectile dysfunction and impotence.

"Pharmaceutically acceptable salts" refer to, alkali metal salts and addition salts of free acids or free bases. Pharmaceutically acceptable salts include, for example, those formed with free amino groups, such as those derived from hydrochloric, hydrobromic, hydroiodide, nitric (nitrate salt), nitrous (nitrite salt), carbonic, phosphoric, sulfuric, acetic, ascorbic, citric, benzoic, formic, fumaric, glycolic, gluconic, glutamic, aspartic, lactic, malic, maleic, propionic, succinic, tartaric, p-toluenesulfonic, methanesulfonic acids, gluconic acid, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesuifonic, sulfanilic, stearic, algenic, hydroxybutyric, cyclohexyl-aminosulfonic, galactaric and galacturonic acid, and the like, and those formed with free carboxyl groups, such as those derived from sodium, potassium, ammonium, aluminum, calcium, ferric hydroxides, lithium, magnesium and zinc or organic salts made from primary, secondary and tertiary amines, cyclic amines, N,N'-dibenzyl-ethylenediamine, chloroprocaine, choline,

diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine and the like. All of these salts may be prepared by conventional means from the corresponding compound by reacting, for example, the appropriate acid or base with the compound.

The present invention is directed to the treatment and/or prevention of sexual dysfunctions in patients, including males and females, by administering the compounds and compositions described herein. The present invention is also directed to enhancing sexual responses in patients, including males and females, by administering the compounds and/or compositions described herein.

Nitric oxide (NO) and NO donors have been recognized as mediators of nonvascular smooth muscle relaxation. As described herein, this effect includes the dilation of the corpus cavernosum smooth muscle, an event involved in the sexual response process for both males and females. However, the effects of NO and NO donor compounds together with α-adrenergic receptor antagonists have not been investigated.

In arriving at the present invention, it was unexpectedly discovered that the risk of toxicities and adverse effects that are associated with high doses of α-adrenergic receptor antagonists can be avoided by the use of such α-adrenergic receptor antagonists in conjunction with one or more compounds that elevate endogenous levels of nitric oxide or endothelium-derived relaxing factor (EDRF) or is a substrate for nitric oxide synthase. Such toxicities and adverse effects include postural hypotension, reflex tachycardia and other arrhythmias, syncope and, with respect to the ergot alkaloids, nausea and vomiting and, upon prolonged or excessive administration, vascular insufficiency and gangrene of the extremities. The α-adrenergic receptor antagonists and compounds that elevate endogenous levels of nitric oxide or EDRF or are substrates for nitric oxide synthase work together to permit the same efficacy with lower doses of the α-adrenergic receptor antagonists or work synergistically to produce an effect that is greater than the additive effects of the α-adrenergic receptor antagonists and the compounds that elevate endogenous levels of nitric oxide or EDRF or are

substrates for nitric oxide synthase.

The α-adrenergic receptor antagonist for use in the present invention can be any known in the art. Preferably, the α-adrenergic receptor antagonist is an imidazoline or an alkaloid.

Imidazolines include phentolamine and tolazoline. Phentolamine is a non-specific α_1 and α_2 adrenergic receptor antagonist. Phentolamine is used in short-term control of hypertension in patients with pheochromocytoma and direct, intracavernous injection of phentolamine (usually in combination with papaverine and PGE_1) has been proposed as a treatment for male sexual dysfunction. Tolazoline is used in the treatment of persistent pulmonary hypertension in neonates. Other imidazolines include, for example, idazoxan, deriglidole, RX 821002, BRL 44408 and BRL 44409 (see, Young et al, *Eur. J. Pharm.*, 168:381-386 (1989), the disclosure of which is incorporated herein by reference). Preferably, the imidazoline is phentolamine. Phentolamine may be provided in a free-base form or in the form of a pharmaceutically acceptable salt. Phentolamine is preferably in the form of phentolamine hydrochloride or phentolamine mesylate, more preferably phentolamine mesylate.

Alkaloids include, for example, yohimban-16-carboxylic acid methyl esters, such as, for example, yohimbine, apoyohimbine, ß-yohimbine, yohimbol, pseudoyohimbine, epi-3α-yohimbine 10-hydroxy-yohimbine and 11-hydroxy-yohimbine, and the like. These compounds are competitive antagonists that are selective for α_2-adrenergic receptors. In humans, these compounds have been observed to increase blood pressure and heart rate and has been used in the treatment of male sexual dysfunction. Preferably the α-adrenergic receptor antagonist is yohimbine, which is the principle alkaloid of the bark of the Corynanthe yohimbine tree. Yohimbine can be provided in the form of a plant extract containing yohimbine, preferably, yohimbe bark powder or yohimbe bark extract. Yohimbine may also be provided in a free-base form or in the form of a pharmaceutically acceptable salt. Yohimbine is preferably in the form of yohimbine hydrochloride, yohimbine tartarate, yohimbe bark powder or

yohimbe bark extract, more preferably yohimbine hydrochloride or yohimbine tartarate. Yohimbine hydrochloride is commercially available, for example, under the trade name Yocon 7 (Glenwood Laboratories, Tenafly, NJ) and Yohimbine Houde (Laboratories Hoechst Houde, France).

Each of the above contemplated α-antagonists is described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Ed.), McGraw-Hill, Inc. (1996), The Physician's Desk Reference (49th Ed.), Medical Economics (1995), Drug Facts and Comparisons (1993 Ed), Facts and Comparisons (1993), Merck Index on CD-ROM, Twelfth Edition, Version 12:1, (1996), STN Express, file phar and file registry, the disclosures of each of which are incorporated herein by reference in their entirety.

The compounds of the present invention that stimulate endogenous synthesis of nitric oxide or elevate levels of endogenous nitric oxide or endothelium-derived relaxing factor (EDRF) *in vivo* or are substrates for nitric oxide synthase can be any such compounds known in the art. Such compounds include, for example, L-arginine and N-hydroxy-L-arginine, including their nitrosated and nitrosylated analogs (e.g., nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, nitrosated L-homoarginine and nitrosylated L-homoarginine), precursors of L-arginine and N-hydroxy-L-arginine and/or physiologically acceptable salts thereof, including for example, citrulline, ornithine, glutamine, lysine, polypeptides comprising at least one of these amino acids, inhibitors of the enzyme arginase (e.g., N-hydroxy-L-arginine and 2(S)-amino-6-boronohexanoic acid) and the substrates for nitric oxide synthase, cytokines, adenosine, bradykinin, calreticulin, bisacodyl, phenolphthalein, and endothelium. EDRF is a vascular relaxing factor secreted by the endothelium, and has been identified as nitric oxide (NO) or a closely related derivative thereof. (Palmer et al, *Nature*, 327:524-526 (1987), Ignarro et al, *Proc. Natl. Acad. Sci. USA*, 84:9265-9269 (1987)).

In the present invention, the preferred compound that stimulates endogenous synthesis of nitric oxide or elevates levels of endogenous nitric oxide or EDRF is L-arginine. L-arginine is an over-the-counter food supplement, and

can be used in free-base form or in the form of a pharmaceutically acceptable salt. L-arginine is preferably in the form of L-arginine hydrochloride or L-arginine glutamate, more preferably L-arginine glutamate. L-arginine glutamate is commercially available from, for example, Teknova, Half Moon Bay, CA; Triple Crown America, Inc., Perkasie, PA; Kelatron Laboratories, Ogden, UT; Advanced Chem Tech, Inc., Louisville, KY; Novartis Pharma SA, France (under the name Dynamisan 7).

In another aspect, the L-arginine can be provided in the free base form in a composition and can be administered to a patient in the form of a pharmaceutically acceptable salt. The composition containing L-arginine free base can further comprise a pharmaceutically acceptable acid. Upon hydration of the L-arginine free base and the pharmaceutically acceptable acid in a liquid , substantially all of the L-arginine free base is converted to its pharmaceutically acceptable salt, based on the pharmaceutically acceptable acid used in the composition. "Substantially all" in this context means that more than about 80% of the L-arginine free base is converted to the pharmaceutically acceptable salt of L-arginine based on the pharmaceutically acceptable acid used in the composition. Preferably about 90%, more preferably about 95%, and most preferably about 100% of the L-arginine free base is converted to the pharmaceutically acceptable salt of L-arginine. The liquid can be any known in the art, such as water, milk, flavored drink, juice, and the like. In this aspect of the invention, the composition preferably comprises L-arginine free base and L-glutamic acid as the pharmaceutically acceptable acid. L-arginine free base and L-glutamic acid are commercially available from, for example, Ajinamoto, Teaneck, NJ; Amresco, Inc., Solon, OH; Bachem Biosciences, King of Prussia, PA; Integra Chemical Company, Renton, WA; Spectrum Quality Products, New Brunswick, NJ. In another embodiment of the invention, the composition comprises L-arginine free base, a pharmaceutically acceptable acid (preferably L-glutamic acid), and a pharmaceutically acceptable salt of L-arginine (preferably L-arginine glutamate).

In another aspect, the present invention provides methods of treating

and/or preventing sexual dysfunctions and/or enhancing sexual responses in a patient in need thereof by administering to the patient a therapeutically effective amount of at least one α-adrenergic receptor antagonist, and at least one compound that elevates levels of endogenous nitric oxide or EDRF *in vivo* or is a substrate for nitric oxide synthase. The compounds can be administered separately or as components of the same composition. The α-antagonist can be any α-antagonist described herein, preferably yohimbine or phentolamine. The compound that elevates endogenous nitric oxide or EDRF or is a substrate for nitric oxide synthase can be any such compound described herein, preferably L-arginine.

The dosage regimen for preventing and/or treating sexual dysfunctions and/or enhancing sexual responses with the compounds and/or compositions of the present invention is selected in accordance with a variety of factors, including the type, age, weight, sex, diet and medical condition of the patient, the severity of the sexual dysfunction, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound used, whether a drug delivery system is used and whether the compound is administered as part of a drug combination. Thus, the dosage regimen actually used may vary widely and therefore may deviate from the preferred dosage regimen set forth herein. Dosage unit compositions may contain such amounts or submultiples thereof to make up the daily dose.

In one embodiment of the present invention, the α-antagonist, such as yohimbine, is administered in an amount of about 1.0 mg to about 18.0 mg (equivalent to about 1.1 mg to about 19.8 mg yohimbine hydrochloride or about 1.4 mg to about 25.6 mg yohimbine tartarate), preferably about 4.5 mg to about 6.4 mg, (equivalent to about 5.0 mg to about 7.0 mg yohimbine hydrochloride or about 6.4 mg to about 9.1 mg yohimbine tartarate), more preferably about 5.0 mg to about 6.0 mg, (equivalent to about 5.5 mg to about 6.5 mg yohimbine hydrochloride or about 7.1 mg to about 8.5 mg yohimbine tartarate), most preferably about 5.5 mg (equivalent to about 6.0 mg yohimbine hydrochloride or

about 7.8 mg yohimbine tartarate). The yohimbine can also be administered in the form of yohimbe bark powder or extract that has been standardized to deliver up to about 18 mg of yohimbine. In conjunction therewith, L-arginine is administered in an amount of about 1 grams to about 10 grams (equivalent to about 2 grams to about 20 grams of L-arginine glutamate), preferably about 2 grams to about 4 grams (equivalent to about 4 grams to about 8 grams of L-arginine glutamate); more preferably about 2.5 grams to about 3.5 grams (equivalent to about 5 grams to about 7 grams of L-arginine glutamate); most preferably about 3.25 grams (equivalent to 6 grams of L-arginine glutamate). Based on the amount of yohimbine in free base form and L-arginine in free base form described herein, one skilled in the art could readily determine the equivalent amount of any particular pharmaceutically acceptable salt of yohimbine or L-arginine.

In another embodiment of the present invention, the α-antagonist, such as phentolamine, is administered in an amount of about 3.7 mg to about 90 mg (equivalent to about 5 mg to about 120 mg phentolamine mesylate), preferably about 22 mg to about 37 mg (equivalent to about 30 mg to about 50 mg phentolamine mesylate), more preferably about 26 mg to about 34 mg (equivalent to about 35 mg to about 45 mg phentolamine mesylate), even more preferably about 28 mg to about 31 mg (equivalent to about 38 mg to about 42 mg phentolamine mesylate), most preferably about 30 mg (equivalent to about 40 mg phentolamine mesylate). In conjunction therewith, L-arginine is administered in an amount of about 0.25 grams to about 10 grams (equivalent to about 0.5 grams to about 20 grams of L-arginine glutamate), preferably about 2 grams to about 4 grams (equivalent to about 4 grams to about 8 grams of L-arginine glutamate); more preferably about 2.5 grams to about 3.5 grams (equivalent to about 5 grams to about 7 grams of L-arginine glutamate); most preferably about 3.25 grams (equivalent to 6 grams of L-arginine glutamate). Based on the amount of phentolamine in free base form and L-arginine in free base form described herein, one skilled in the art could readily determine the equivalent amount of any particular pharmaceutically acceptable salt of phentolamine or L-arginine.

The compounds of the present invention can be administered orally, bucally, parenterally, topically or rectally in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles, as desired. Preferably, the compounds and/or compositions are administered orally.

Solid dosage forms for oral administration can include capsules, tablets, chewable tablets, wafers, pills, effervescent tablets, powders, effervescent powders, gels, lozenges, troches, and encapsulated powders. "Powder" as used herein includes both powders and granules. In such solid dosage forms, the active compound(s) may be admixed with at least one inert diluent or carrier, such as sucrose lactose or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, chewable tablets, effervescent tablets, powders and pills, the dosage forms may also comprise buffering agents. Tablets and pills can also be prepared with enteric coatings. Solid dosage forms can also comprise sweetening and flavoring agents. Powders can also comprise anti-caking agents, such as cellulose.

Effervescent tablets and effervescent powders can be prepared by methods known in the art. For example, effervescent tablets and effervescent powders preferably comprise an acidic component (such as, for example, citric acid, fumaric acid, tartaric acid, adipic acid, and the like), and an alkaline component (such as, for example, sodium carbonate, potassium carbonate, calcium carbonate, sodium bicarbonate, potassium bicarbonate, and the like) that in the presence of moisture react to form gaseous carbon dioxide.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

The compositions of the present invention can also include other components, including, for example, vitamins (such as, for example, Vitamin A,

Vitamin C, Vitamin E, Vitamin B-5, thiamin, riboflavin, and the like); minerals (such as, for example, zinc, selenium, and the like); plant extracts (such as, for example, Ginkgo, Ginseng, Saw Palmetto berry, St. John's Wort, Avena Sativa, and the like); anti-oxidants (such as, for example, ascorbic acid, and the like); hormones (such as, for example, dehydroepiandrosterone, and the like); and amino acids (such as, for example, L-tyrosine, and the like).

The compounds and compositions of the present invention will typically be administered in a pharmaceutical composition containing one or more carriers or excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances which do not deleteriously react with the active compounds. Examples of pharmaceutically acceptable carriers include, for example, water, salt solutions, alcohol, silicone, waxes, petroleum jelly, vegetable oils, polyethylene glycols, propylene glycol, liposomes, sugars, gelatin, lactose, amylose, magnesium stearate, talc, surfactants, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethyl-cellulose, polyvinylpyrrolidone, and the like. The pharmaceutical preparations can be sterilized and if desired, mixed with auxiliary agents which do not deleteriously react with the active compounds, e.g., preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavoring and/or aromatic substances, and the like. Aqueous suspensions may contain substances which increase the viscosity of the suspension and include, for example, sodium carboxymethyl cellulose, sorbitol and/or dextran. Optionally, the suspension may also contain stabilizers.

The composition, if desired, can also contain minor amounts of wetting agents, emulsifying agents and/or pH buffering agents. The composition can be a liquid solution, suspension, emulsion, tablet, effervescent tablet, pill, capsule, sustained release formulation, powder or effervescent powder. Oral formulations can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like.

Various delivery systems are known and can be used to administer the compounds or compositions of the present invention, including, for example, encapsulation in liposomes, microbubbles, emulsions, microparticles, microcapsules and the like. The required dosage can be administered as a single unit or in a sustained release form.

The bioavailability of the compositions can be enhanced by micronization of the formulations using conventional techniques such as grinding, milling, spray drying and the like in the presence of suitable excipients or agents such as phospholipids or surfactants.

In one embodiment of the present invention, the α-antagonist (such as yohimbine or phentolamine) and L-arginine are administered as separate components. Preferably, the α-antagonist (such as yohimbine or phentolamine) is administered in the form of an oral tablet (or effervescent tablet) or powder (or effervescent powder); and L-arginine is prepared either in the form of an oral tablet (or effervescent tablet) or powder (or effervescent powder) that is dissolved in a liquid before being orally ingested. When the α-antagonist and L-arginine are administered as separate components in the methods of the present invention, they are preferably administered to the patient at about the same time. "About the same time" means that within about thirty minutes of administering one compound (e.g., the α-antagonist or L-arginine) to the patient, the other compound (e.g., L-arginine or the α-antagonist) is administered to the patient. "About the same time" also includes simultaneous administration of the compounds.

In another embodiment of the present invention, the α-antagonist (such as yohimbine or phentolamine) and L-arginine are components in the same composition. The composition may be in the form of a powder (or effervescent powder) or tablet (or effervescent tablet), wherein the powder or tablet can be dissolved in a liquid before being orally ingested. In either case, the powder (or effervescent powder) or tablet (or effervescent tablet) are capable of dissolving in a liquid to form a solution or suspension. The powder (or effervescent powder)

or tablet (or effervescent tablet) can be vigorously stirred in the liquid to facilitate dissolution. The liquid can be any known in the art, such as water, milk, flavored drink, juice, and the like.

While the compounds and/or compositions of the present invention may be administered on a regular basis, they are preferably administered as a single dose prior to sexual activity or sexual intercourse. Such single dose administration prior to sexual activity or sexual intercourse allows for the prevention and/or treatment of a sexual dysfunction in a patient and/or enhances sexual responses in a patient.

For example, in the methods of the present invention, the compound(s) and/or composition(s) are generally administered about 15 minutes to about 125 minutes prior to sexual activity or sexual intercourse; preferably about 30 minutes to about 90 minutes prior to sexual activity or sexual intercourse; more preferably about 45 minutes to about 75 minutes prior to sexual activity or sexual intercourse; even more preferably about 50 minutes to about 70 minutes prior to sexual activity or sexual intercourse; still more preferably about 55 minutes to about 65 minutes prior to sexual activity or sexual intercourse; most preferably about 60 minutes prior to sexual activity or sexual intercourse.

While the compounds and/or compositions of the present invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more other compounds that are known to be effective against sexual dysfunctions, including, for example, vasoactive agents. Exemplary vasoactive agents include potassium channel activators, calcium channel blockers, α-adrenergic receptor antagonists, β-blockers, phosphodiesterase inhibitors, adenosine, ergot alkaloids, vasoactive intestinal peptides, prostaglandins, opioid antagonists, endothelin antagonists, dopamine agonists, and the like.

The present invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compounds of the present invention. Associated with such kit(s) or container(s) can be a notice in the form prescribed by a governmental

agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

In a preferred embodiment, the compounds and/or compositions of the present invention are packaged for distribution in a sachet. The sachet can be made of any material known in the art including, for example, plastic, MYLAR®, foil, paper, and the like. The sachet is preferably made of a moisture-resistant material. The compounds and/or compositions of the present invention are removed from the sachet prior to being administered to the patient. For ease of use and administration by the patient, each sachet preferably contains a single dose of the compounds and/or compositions of the present invention.

EXAMPLE

The following non-limiting example further describes and enables one of ordinary skill in the art to make and use the invention. The example is for purposes of illustration only and is not intended to limit the scope of the invention or claims.

Example 1: Administration of yohimbine hydrochloride and L-arginine glutamate for the treatment of male sexual dysfunction

A comparative Phase II double blind with double placebo, randomized and controlled single-center study was conducted to determine the efficacy of yohimbine hydrochloride and L-arginine glutamate for the treatment of male sexual dysfunction. Forty eight patients suffering from erectile dysfunction for at least 3 months were identified by a hospital's urology department. The initial evaluation of each patient included a physical examination and a questionnaire-derived sexual history. The questionnaire was self-administered, and the validated International Index of Erectile Function (IIEF) was used to measure the attributes. The median age of the patients was 57 years and none of the patients had any known sensitivity to either yohimbine or L-arginine. The patients were divided into 6 groups of 8 patients each. The overall composition of each group was as closely matched as possible.

There were 3 treatment periods, each lasting 14 days, for a total of 42 days

of treatment. The 3 treatment periods were (i) yohimbine hydrochloride and L-arginine glutamate, (ii) yohimbine hydrochloride and L-arginine placebo, and (iii) yohimbine placebo and L-arginine placebo. The yohimbine hydrochloride was administered as a single dose of 6 mg yohimbine hydrochloride. The L-arginine glutamate was administered as a single dose of 6 grams arginine glutamate in a drink. The L-arginine and yohimbine placebos were packaged in the same form as the pharmacologically active components. Each patient group was given the 3 treatment regimes in a random order. The patients were instructed to take no more than one treatment per day, on demand, 1-2 hours before sexual intercourse. The patients kept a detailed dairy and were required to complete the IIEF questionnaire at the end of each treatment period. The patients took the entire fourteen day period into consideration when giving the average rating to the 15 questions.

Of the forty-eight patients enrolled, three patients withdrew from the study prematurely. The results of the remaining forty-five patients were analyzed statistically. Two important IIEF domains were improved for patients with an IIEF score above 14 by the treatment with the combination of yohimbine and L-arginine: the erectile function domain and the global satisfaction domain.

The erectile function domain had a value of (i) 19.83 ± 1.038 for yohimbine hydrochloride and L-arginine glutamate, (ii) 16.64 ± 1.053 for yohimbine hydrochloride and L-arginine placebo, and (iii) 15.91 ± 1.060 for yohimbine placebo and L-arginine placebo. The combination of yohimbine and arginine was significantly better than the yohimbine placebo and L-arginine placebo ($p = 0.0298$) and the yohimbine hydrochloride and L-arginine placebo ($p = 0.0089$).

The global satisfaction domain had a value of (i) 5.56 ± 0.261 for yohimbine hydrochloride and L-arginine glutamate, (ii) 4.82 ± 0.261 for yohimbine hydrochloride and L-arginine placebo, and (iii) 4.70 ± 0.261 for yohimbine placebo and L-arginine placebo. The combination of yohimbine and arginine was significantly better than the yohimbine placebo and L-arginine placebo ($p = 0.0219$) and the yohimbine hydrochloride and L-arginine placebo ($p = 0.0474$).

The disclosure of each patent, patent application and publication cited or described in the specification is hereby incorporated by reference herein in its entirety.

Although the invention has been set forth in detail, one skilled in the art will appreciate that numerous changes and modifications can be made to the invention without departing from the spirit and scope thereof.

CLAIMS

What is claimed is:

1. A sachet comprising an orally administrable single dose composition comprising L-arginine and/or a pharmaceutically acceptable salt thereof in an amount of about 1 gram to about 10 grams based on the free base form of L-arginine, and yohimbine or a pharmaceutically acceptable salt thereof in an amount of about 1 milligram to about 18 milligrams based on the free base form of yohimbine.

2. The sachet of claim 1, wherein the L-arginine and/or the pharmaceutically acceptable salt thereof is L-arginine hydrochloride, L-arginine glutamate or a mixture thereof.

3. The sachet of claim 1 or 2, wherein the L-arginine and/or the pharmaceutically acceptable salt thereof is L-arginine glutamate in an amount of about 2 grams to about 20 grams.

4. The sachet of claim 3, wherein the L-arginine glutamate is present in an amount of 5 grams to about 7 grams.

5. The sachet of claim 1, wherein the yohimbine or the pharmaceutically acceptable salt thereof is yohimbine hydrochloride, yohimbine tartarate or a mixture thereof.

6. The sachet of claim 1 or 5, wherein the yohimbine or the pharmaceutically acceptable salt thereof is yohimbine hydrochloride in an amount of about 1.1 milligrams to about 19.8 milligrams.

7. The sachet of claim 6, wherein the yohimbine hydrochloride is present in an amount of about 5.5 milligrams to about 6.5 milligrams.

8. The sachet of claim 1 or 5, wherein the yohimbine or the pharmaceutically acceptable salt thereof is yohimbine tartarate in an amount of about 1.4 milligrams to about 25.6 milligrams.

9. The sachet of claim 8, wherein the yohimbine tartarate is present in an amount of about 7.1 milligrams to about 8.5 milligrams.

10. The sachet of claim 1, wherein the yohimbine is in the form of a yohimbe bark powder, a yohimbe bark extract, a plant extract containing

yohimbine or a mixture thereof.

11. The sachet of claim 10, wherein the yohimbine in the yohimbe bark powder, the yohimbe bark extract, the plant extract containing yohimbine or a mixture thereof is present in an amount of up to about 18 mg standardized to yohimbine.

12. The sachet of claim 1, wherein the orally administrable single dose composition is a solid dose.

13. The sachet of claim 12, wherein the solid dose is a tablet, a capsule or a powder.

14. The sachet of claim 12, wherein the solid dose is an effervescent tablet or an effervescent powder.

15. The sachet of claim 1, wherein the orally administrable single dose composition is a solution, a suspension or an emulsion.

16. The sachet of claim 1, further comprising at least one vasoactive agent or a pharmaceutically acceptable salt thereof.

17. The sachet of claim 16, wherein the vasoactive agent is a potassium channel activator, a calcium channel blocker, an α-blocker, a β-blocker, a phosphodiesterase inhibitor, adenosine, an ergot alkaloid, a vasoactive intestinal peptide, a prostaglandin, an opioid antagonist, an endothelin antagonist, a dopamine agonist or a mixture thereof.

18. Use of L-arginine and/or a pharmaceutically acceptable salt thereof in an amount of about 1 gram to about 10 grams based on the free base form of L-arginine and yohimbine or a pharmaceutically acceptable salt thereof in an amount of about 1 milligram to about 18 milligrams based on the free base form of yohimbine for the production of an orally administrable single dose composition in a sachet for treating a sexual dysfunction or enhancing a sexual response in a patient.

19. The use of claim 18, wherein the L-arginine and/or the pharmaceutically acceptable salt thereof is L-arginine hydrochloride, L-arginine glutamate or a mixture thereof.

20. The use of claim 18 or 19, wherein the L-arginine and/or the pharmaceutically acceptable salt thereof is L-arginine glutamate in an amount of about 2 grams to about 20 grams.

21. The use of claim 20, wherein the L-arginine glutamate is present in an amount of 5 grams to about 7 grams.

22. The use of claim 18, wherein the yohimbine or the pharmaceutically acceptable salt thereof is yohimbine hydrochloride, yohimbine tartarate or a mixture thereof.

23. The use of claim 18 or 22, wherein the yohimbine or the pharmaceutically acceptable salt thereof is yohimbine hydrochloride in an amount of about 1.1 milligrams to about 19.8 milligrams.

24. The use of claim 23, wherein the yohimbine hydrochloride is present in an amount of about 5.5 milligrams to about 6.5 milligrams.

25. The use of claim 18 or 22, wherein the yohimbine or the pharmaceutically acceptable salt thereof is yohimbine tartarate in an amount of about 1.4 milligrams to about 25.6 milligrams.

26. The use of claim 25, wherein the yohimbine tartarate is present in an amount of about 7.1 milligrams to about 8.5 milligrams.

27. The use of claim 18, wherein the yohimbine is in the form of a yohimbe bark powder, a yohimbe bark extract, a plant extract containing yohimbine, or a mixture thereof.

28. The use of claim 27, wherein the yohimbine in the yohimbe bark powder, the yohimbe bark extract, the plant extract containing yohimbine, or a mixture thereof is present in an amount of up to about 18 mg standardized to yohimbine.

29. The use of claim 18, wherein the orally administrable single dose composition is a solid dose.

30. The use of claim 29, wherein the solid dose is a tablet, a capsule or a powder.

31. The use of claim 29, wherein the solid dose is an effervescent tablet

or an effervescent powder.

32. The use of claim 18, wherein the orally administrable single dose composition is a solution, a suspension or an emulsion.

33. The use of claim 18, further comprising at least one vasoactive agent or a pharmaceutically acceptable salt thereof for the production of an orally administrable single dose composition.

34. The use of claim 33, wherein the vasoactive agent is a potassium channel activator, a calcium channel blocker, an α-blocker, a β-blocker, a phosphodiesterase inhibitor, adenosine, an ergot alkaloid, a vasoactive intestinal peptide, a prostaglandin, an opioid antagonist, an endothelin antagonist. A dopamine agonist or a mixture thereof.

35. A method for treating a sexual dysfunction or enhancing a sexual response in a patient in need thereof comprising orally administering a single dose composition comprising L-arginine and/or a pharmaceutically acceptable salt thereof in an amount of about 1 gram to about 10 grams based on the free base form of L-arginine and yohimbine or a pharmaceutically acceptable salt thereof in an amount of about 1 milligram to about 18 milligrams based on the free base form of yohimbine to the patient about 1 minute to about 125 minutes prior to sexual activity or sexual intercourse.

36. The method of claim 35, further comprising removing the single dose composition from a sachet prior to administering the single dose composition to the patient.

37. The method of claim 35, wherein the single dose composition is administered to the patient about 30 minutes to about 90 minutes prior to sexual activity or sexual intercourse.

38. The method of claim 35, wherein the L-arginine and/or the pharmaceutically acceptable salt thereof is L-arginine hydrochloride, L-arginine glutamate or a mixture thereof.

39. The method of claim 35 or 38, wherein the L-arginine and/or the pharmaceutically acceptable salt thereof is L-arginine glutamate in an amount of about 2 grams to about 20 grams.

40. The method of claim 39, wherein the L-arginine glutamate is present in an amount of 5 grams to about 7 grams.

41. The method of claim 35, wherein the yohimbine or the pharmaceutically acceptable salt thereof is yohimbine hydrochloride, yohimbine tartarate or a mixture thereof.

42. The method of claim 35 or 41, wherein the yohimbine or the pharmaceutically acceptable salt thereof is yohimbine hydrochloride in an amount of about 1.1 milligrams to about 19.8 milligrams.

43. The method of claim 42, wherein the yohimbine hydrochloride is present in an amount of about 5.5 milligrams to about 6.5 milligrams.

44. The method of claim 35 or 41, wherein the yohimbine or the pharmaceutically acceptable salt thereof is yohimbine tartarate in an amount of about 1.4 milligrams to about 25.6 milligrams.

45. The method of claim 44, wherein the yohimbine tartarate is present in an amount of about 7.1 milligrams to about 8.5 milligrams.

46. The method of claim 35, wherein the yohimbine is in the form of a yohimbe bark powder, a yohimbe bark extract, a plant extract containing yohimbine, or a mixture thereof.

47. The method of claim 46, wherein the yohimbine in the yohimbe bark powder, the yohimbe bark extract, the plant extract containing yohimbine, or a mixture thereof is present in an amount of up to about 18 mg standardized to yohimbine.

48. The method of claim 35, wherein the orally administrable single dose composition is a solid dose.

49. The method of claim 48, wherein the solid dose form is a tablet, a capsule or a powder.

50. The method of claim 48, wherein the solid dose is an effervescent tablet or an effervescent powder.

51. The method of claim 35, wherein the orally administrable single dose composition is a solution, a suspension or an emulsion.

52. The method of claim 35, wherein the patient is male or female.

53. The method of claim 35, further comprising administering at least one vasoactive agent or a pharmaceutically acceptable salt thereof.

54. The method of claim 53, wherein the vasoactive agent is a potassium channel activator, a calcium channel blocker, an α-blocker, a β-blocker, a phosphodiesterase inhibitor, adenosine, an ergot alkaloid, a vasoactive intestinal peptide, a prostaglandin, an opioid antagonist, an endothelin antagonist, a dopamine agonist or a mixture thereof.

55. An orally administrable effervescent tablet comprising L-arginine and/or a pharmaceutically acceptable salt thereof in an amount of about 1 gram to about 10 grams based on the free base form of L-arginine and yohimbine or a pharmaceutically acceptable salt thereof in an amount of about 1 milligram to about 18 milligrams based on the free base form of yohimbine.

56. An orally administrable effervescent powder comprising L-arginine and/or a pharmaceutically acceptable salt thereof in an amount of about 1 gram to about 10 grams based on the free base form of L-arginine and yohimbine or a pharmaceutically acceptable salt thereof in an amount of about 1 milligram to about 18 milligrams based on the free base form of yohimbine.

57. A method of treating a sexual dysfunction or enhancing a sexual response in a patient in need thereof comprising:

providing a composition comprising a therapeutically effective amount of L-arginine free base, yohimbine or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable acid,

mixing the composition with a liquid wherein substantially all of the L-arginine free base is converted to the pharmaceutically acceptable salt thereof based on the pharmaceutically acceptable acid in the composition; and

administering the resulting mixture to the patient.

58. The method of claim 57, further comprising removing the composition from a sachet to prior to mixing the liquid with the composition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/06437

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A01N 43/42; A61K 31/00, 31/44, 31/195, 31/475
US CL :514/280, 565, 754, 968

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/280, 565, 754, 968

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim
X - Y	WO 99/01132 A1 (REAL 2000 LIMITED) 19 JANUARY 1999, see entire document.	1-15,18-32,35 and 55-58 16-17, 33-34 ; 53-54
Y	US 5,565,466 A (GIOCO et al.) 15 OCTOBER 1996, see especially col. 3-4; and patent claims.	1-58
Y	US 5,731,339 A (LOWREY, F.) 24 MARCH 1998, see entire document.	1-58
Y,P	US 5,910,316 A (KIEFER et. al.) 08 JUNE 1999, see entire document.	1-58

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or prior date and not in conflict with the application but cited to understa the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot b considered novel or cannot be considered to involve an inventive st when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot b considered to involve an inventive step when the document combined with one or more other such documents, such combinatio being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 25 MAY 2000	Date of mailing of the international search report 29 JUN 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer BENNETT CELSA Telephone No. (703) 308-0196

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/06437

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SONDA, L.P. et al. The Role of Yohimbine for the Treatment of Erectile Impotence. J. Sex & Marital Ther. Spring 1990, Vol. 16, No. 1, pages 25-21, see entire article.	1-58
Y	ZORGNIOTTI, A.W. et al. Effect of Large Doses of the Nitric Oxide Precursor L-Arginine. On Erectile Dysfunction. Int. J. Impotence Res. 1994, Vol. 6, pages 33-36, see entire article.	1-58